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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/535,390	03/24/2000	Balaram Ghosh	U 012673-3	2390

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EXAMINER

KWON, BRIAN YONG S

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	09/535,390		GHOSH ET AL.	
	Examiner		Art Unit	
	Brian S. Kwon		1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-17 is/are pending in the application.
- 4a) Of the above claim(s) 2-8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1614

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.
2. Although the claim 1 is presented in the instant application with identification "Previously Presented", the claim 1 was previously cancelled (see Applicant's Response filed December 09, 2002).
3. Claims 2-17 are pending in the application, but claims 2-8 were withdrawn from further consideration by Examiner as being drawn to the non-elected invention.
4. Claims 9-17 are currently pending for prosecution on the merits.

Specification

5. Acknowledgement is made of applicant's filing of drawings (16 sheets of drawing: Figure 1, Figure 2(a), 2(a)1-3, Figure 2(b), Figure 2(b)1-3, Figure 2(c), Figure 2(c)1-5 and Figure 3). The specification is objected to because no brief description of the drawings for 2(a)1-3, 2(b)1-3 and 2(c)1-5 is present. Correction is requested.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

Art Unit: 1614

the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 14-15 are rejected under 35 USC 102(b) as being anticipated by Aggarwal (WO 970877).

Aggarwal teach a use of curcumin in treating septic shock condition, wherein said curcumin is administered in a dose of from about 1mg/kg to about 100mg/kg (page 1, line 21 thru page 2, line 2; page 2, lines 13-15; Claims 1 and 3).

Although Aggarwal is silent about the underlying mechanism of “controlling neutrophil infiltration”, such underlying pharmacological mechanism must be inherently presented in the referenced method since the prior art method employs the same compound (i.e., curcumin) in the overlapping concentration for the same ultimate purpose. It is noted to applicants that the prior art directing the administration of same compound inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by Applicants anticipates the claimed invention even absent explicit recitations of the mechanism of action.

Claim Rejections - 35 USC § 103

Art Unit: 1614

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 9-12 and 16 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Ammon et al. (US 5401777).

The teaching of Aggarwal has been discussed in above 35 USC 102(b) rejection.

Ammon teaches an oral dosage form of curcumin including suspension wherein the oral dosage form is prepared in non-toxic organic solvent or oil (abstract; column 7, lines 3-34).

The teaching of Aggarwal differs from the claimed invention in (i) oral administration, specifically "orally as a suspension in pharmacologically acceptable non-toxic organic solvent or oil"; (ii) the specific time intervals; (iii) "observing every two or three hours for septic shock"; and (iv) "probing reduction in neutrophil infiltration from blood vessels to the underlying tissue by staining and microscopically examining the extent of inflammation".

However, it would have been obvious to one having ordinary skill in the art since the claimed oral administration of curcumin is well known in the art. The above references in

Art Unit: 1614

combination make clear that the administration of curcumin for the treatment of inflammatory condition such as septic shock condition is old and well known. The above references in combination also make clear that the administration of curcumin in the oral dosage form is old and well known. One having ordinary skill in the art would have been motivated to make such modification to extend the usage of curcumin in readily available oral dosage form to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated dosage regimen.

The prior art does not disclose the required specific time interval and "observing every two to three hours". However, differences in time interval requirements or time periods will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such time periods is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable time periods by routine experimentation.

The prior art does not disclose the required step of "probing reduction in neutrophil infiltration from blood vessels to the underlying tissue by staining and microscopically examining the extent of inflammation". However, such probing technique will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such probing technique is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the probing technique by routine experimentation.

9. Claims 13 and 17 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Schneider (US 6013273).

The teaching of Aggarwal has been discussed in above 35 USC 102(b) rejection.

Art Unit: 1614

Schneider et al. (US 6013273) teaches the use of antioxidant in treating septic or endotoxin shock (column 4, lines 51-53).

The teaching of Aggarwal differs from the claimed invention in combination with an antioxidant preparation. To incorporate such teaching into the teaching of Aggarwal, would have been obvious in view of Schneider et al. who teaches the use of antioxidant in treating septic shock.

Above references in combination make clear that curcumin and antioxidant have been individually used for the treatment of septic (or endotoxin) shock. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

The above references in combination make clear that the combination of curcumin and antioxidant for the treatment of septic shock is old and well known. One having ordinary skill in the art would have been motivated to do so such that such combination provides enhanced activity in treating septic shock while minimizing adverse effects.

As stated above, the prior art does not disclose the underlying pharmacological mechanism of curcumin in "controlling neutrophil infiltration". However, the fact that the applicant may have discovered a new pharmacological mechanism for curcumin is not considered patentably distinctive over the prior art which are directed to the same therapeutic application (for the treatment of septic shock condition).

Response to Arguments

10. Applicant's arguments filed April 20, 2006 have been fully considered but they are not persuasive.

Applicant's argument in the response, which is similar to November 24, 2004, takes the position that Aggarwal does not guide, indicate nor show any experiment or supporting data whatsoever which would lead to the applicant's discovery of the activity of curcumin in preventing neutrophil infiltration leading to treatment or prevention of septic shock.

This argument is not found persuasive. Although the Examiner agrees that none of prior art cited by the examiner specifically discloses the underlying pharmacological mechanism of curcumin in inhibiting neutrophil infiltration from blood vessels to underlying tissues, the prior art directing the administration of same compound (i.e., curcumin), in overlapping dosage amounts, inherently possessing a therapeutic effect for the same ultimate purpose (i.e., septic shock) as disclosed by Applicants anticipates the claimed invention even absent explicit recitations of the mechanism of action.

In response to the applicant's argument that Aggarwal provides no evidence that inhibition of NF-kB activation by curcumin would provide efficacy in treating toxic/septic shock, the examiner recognizes that the whole context of Aggarwal teaches the activity of curcumin in inhibiting TNF-dependent activation of NF-kB or NF-kB transcription factor such as p65 subunit of NF-kB transcription factor (see page 2, lines 26-29; page 3, lines 7-25; Figures 1 and 6; page 11, lines 3-7; page 12, lines 27 thru page 13, 11; page 13, lines 23-24) and the involvement of NF-kB in pathogenesis of various conditions including toxic/septic shock (page

Art Unit: 1614

1, lines 21-25; page 6, lines 1-25; claims 1-8). Similar to the Aggarwal, the involvement of NF-kB activation as a pathological mechanism of septic shock and inflammation is well recognized in the art ("Inhibition of NF-kB activation by pyrrolidine dithiocarbamate prevents in vivo expression of proinflammatory genes, Liu et al., Circulation, 1999, abstract, Vol. 100, No. 12, pp. 1330-1337; "NF-kB activation as a pathological mechanism of septic shock and inflammation", Liu et al., Am J Physiology Lung Cell Mol Physiol 290: L622-L645, 2006; US 5981583; US 6545027). Thus, one having ordinary skill in the art is able to "at once envisage" the claimed utility of treating toxic/septic shock with the administration of curcumin having the blocking activity of NF-kB activation.

Anticipation under 35 USC 102 is an essentially irrebuttable question of fact, wherein the court stated that anticipation "cannot be overcome by evidence of unexpected results or teachings away in the art". *In re Malagari*, 499 F.2d 1289, 182 USPQ; *In re Spada*, 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990); *In re Fracalossi*, 681 F.2d 792, 215 USPQ 569 (CCPA 1982); *In re Altermohl*, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973); *In re Wilder*, 429 F.2d 447, 166 USPQ 545 (CCPA 1970). Indeed, a reference might reside in a nonanalogous art and yet constitute an anticipation of a claimed invention under 35 USC 102. *In re Self*, 571 F.2d 134, 213 USPQ 1 (CCPA 1982).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

Art Unit: 1614

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As discussed above, Aggarwal et al. teaches the claimed invention. Therefore, one having ordinary skill in the art would have been motivated to combine the references and make such modification to extend the usage of curcumin to (i) accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated or concurrent dosage regimen (ii) to provide enhanced activity of the drug in treating septic shock while minimizing adverse effects by combining two compositions each of which is taught by prior art to be useful for the same purpose. Those of ordinary skill in the art would have been readily optimized effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information herein. The final dosage regimen would have been determined by the attending physician, considering the drug's specific activity, the responsiveness of the subject, the age, condition, body weight, diet, the severity of any infection, time of administration and other clinical factors. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients

Art Unit: 1614

and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

11. No Claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see <http://pair-direct.uspto.gov> Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon

Primary Patent Examiner

AU 1614

A handwritten signature in black ink, appearing to be 'B. Kwon', with a long horizontal line extending to the right.